



# A POLICY ANALYSIS OF HOW FDA SHOULD REGULATE HUMAN BONE MARROW TRANSPLANTATION

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## **A POLICY ANALYSIS OF HOW FDA SHOULD REGULATE HUMAN BONE MARROW TRANSPLANTATION**

### **I. INTRODUCTION**

Over the past twenty years, physicians have carried out bone marrow transplants with increasing success.<sup>1</sup> As the procedure gains in acceptance and availability over the coming years, our nation will be faced with important policy choices regarding the regulation of bone marrow transplantation.

This essay begins with a brief recitation of the biology of bone marrow transplantation, a description of the risks involved, and an introduction to the National Marrow Donor Program. The focus of the essay then shifts to a policy analysis of how the Food and Drug Administration (FDA) should regulate bone marrow transplantation. Overriding considerations are protection of the public health and efficiency in implementing new regulations. An effective regulatory scheme should ensure minimum protections for marrow recipients and donors without significantly impacting the resources of regulated parties or FDA itself.

<sup>1</sup>H.G. DEEG, A GUIDE TO BONE MARROW TRANSPLANTATION, preface (1988).

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**A. Biology of bone marrow and bone marrow transplantation**

As producer of the body's blood, healthy bone marrow is necessary for human life.<sup>2</sup> Unfortunately, bone marrow is extremely sensitive to toxins and drugs.<sup>3</sup> For example, leukemia patients treated with chemoradiotherapy may subsequently require bone marrow transplantation.<sup>4</sup> Bone marrow transplantation may also be used to cure other malignancies and some hereditary diseases.<sup>5</sup>

The two main forms of bone marrow transplantation are autologous and allogeneic.<sup>6</sup> The more common form is autologous bone marrow transplantation,<sup>7</sup> in which the patient's own marrow is stored, sometimes treated, and then returned to the patient.<sup>8</sup> Allogenic bone marrow transplantation involves transplanting bone marrow from a

<sup>2</sup>ELI<sup>+</sup> MARGET, LIFE'S BLOOD 21 (1992)

<sup>3</sup>.*rd.*

<sup>4</sup>DEEG, *supra* note 1, at preface.

<sup>5</sup>MARGET, *supra* note 2, at 13.

<sup>6</sup>Jacob M. Rowe, et. al., *Recommended Guidelines for the Management of Autologous and Allogeneic Bone Marrow Transplantation: A Report from the Eastern Cooperative Oncology Group (ECOG)*, 120 ANNALS OF INTERNAL MED. 143, 143 (1994)

<sup>7</sup>.

<sup>8</sup>See 57 Fed. Reg. 24,797, 24,803 (June 11, 1992)

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donor to a recipient who suffers from a marrow deficiency or defect.<sup>9</sup>

**B. Risks of bone marrow transplantation**

The risks of bone marrow transplantation are extreme. For example, inadequately purging the bone marrow of a cancer patient undergoing an autologous bone marrow transplant can result in relapse of the cancer.<sup>10</sup> The recipient of an allogeneic bone marrow transplant faces the risk of contracting an infectious disease such as Acquired Immune Deficiency Syndrome (AIDS).<sup>11</sup> In addition, a recipient faces the risk of graft-versus-host disease (GVHD), which can be fatal.<sup>12</sup>

GVHD results when cells derived from the immune system of the donor attack cells of the recipient.<sup>13</sup> Successful bone marrow transplantation requires close matching of a particular gene, or HLA matching.<sup>14</sup> Because HLA type is an inherited characteristic,<sup>15</sup> a marrow transplant from one

9.

<sup>10</sup> See Ralph O. Wallerstein, Jr. and Albert B. Deisseroth, *Bone Marrow Dysfunction in the Cancer Patient in* CANCER: PRINCIPLES AND PRACTICE OF ONCOLOGY 2262, 2272 (4th ed. 1993)

<sup>11</sup> National Marrow Donor Program Standards 4.122 (11th ed., adopted 10/28/94) [hereinafter NMDP Standards]

<sup>12</sup> GET, *supra* note 2, at 33.

<sup>13</sup> DEEG, *supra* note 1, at 191.

<sup>14</sup> See *e.g.*, CURRENT MEDICAL DIAGNOSIS & TREATMENT 627 (Lawrence M.

Tierney, Jr. et. al. eds., 1993).

<sup>15</sup> NATIONAL MARROW DONOR PROGRAM, REPORT TO OUR COMMUNITIES 1 (1994) [hereinafter NATIONAL MARROW DONOR PROGRAM REPORT]

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identical twin to another will almost certainly not result in GVHD.<sup>16</sup> Patients in need of an allogeneic marrow transplant may sometimes find a sufficient ELA match in another close relative such as a non-identical sibling.<sup>17</sup> Unfortunately, however, only twenty to thirty percent of patients in need of an allogeneic marrow transplant have an HLA-matching relative.<sup>18</sup> The National Marrow Donor Program assists patients in searching for nonrelated marrow donors, as will be discussed in the following Section.

Although donation by a prospective donor with existing health conditions may constitute a major physical risk to that donor, the risk of a serious complication in a healthy donor is negligible.<sup>19</sup> All donors, however, face minor physical risks. For example, the procedure by which marrow is withdrawn from the pelvis can be painful.<sup>20</sup> In addition, the donor may be fatigued for up to several weeks while the donor's marrow regenerates.<sup>21</sup>

<sup>16</sup>A~GET, *supra* note 2, at 32.

<sup>17</sup>See DEEG, *supra* note 1, at preface.

<sup>18</sup>Nancy A. Kernan, et. al., *Analysis of 462 Transplantations from Unrelated Donors Facilitated by the National Marrow Donor Program*, 328 NEW ENG. J. MED. 593, 593 (1993)

<sup>19</sup>MARGET, *supra* note 2, at 36.

<sup>20</sup>*Id*

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### C. National Marrow Donor Program

In 1986, Congress established the National Marrow Donor Program (NMDP) to facilitate the matching of potential recipients with nonrelated donors.<sup>22</sup> During the program's first four years, 462 patients received marrow transplants from unrelated donors.<sup>23</sup> In 1993, NMDP celebrated the enlistment of the one millionth volunteer donor on the registry.<sup>24</sup> Because of this success in recruiting volunteers, fifty-six percent of potential recipients find a perfectly HLA-matched donor.<sup>25</sup> NMDP plans to continue to expand the registry so that more patients in need of marrow will be able to find HLA-matching donors.<sup>26</sup>

In addition to the donor registry, Congress directed NMDP to establish criteria for those centers participating in the program, including marrow donor centers, marrow collection centers, and marrow transplant centers.<sup>27</sup> Among other requirements, these standards must include:

- (1) quality standards and standards for tissue typing, obtaining the informed consent of donors, and providing patient advocacy;
- (2) donor selection criteria, based on established medical criteria<sup>1</sup> to protect both the donor and the

2242 U.S.C. § 274k. See *also* Kernan, *supra* note 18, at 593.

<sup>23</sup>Kernan, *supra* note 18, at 593.

<sup>24</sup>NATIONAL MARROW DONOR PROGRAM REPORT, *supra* note 15, at preface.

<sup>25</sup>*Id.* at 1.

<sup>26</sup>See *id.*

2742 U.S.C. § 247k(c).

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recipient and to prevent the transmission of potentially harmful infectious diseases such as the viruses that cause hepatitis and the etiologic agent for Acquired Immune Deficiency Syndrome.

(3) procedures to ensure the proper collection and transportation of the marrow.... 28

NMDP established a set of standards which are now in their Eleventh Edition.<sup>29</sup> Since these standards apply only to centers participating in NMDP, however, centers which do not participate in NMDP are not regulated at all. The remainder of this essay considers whether FDA should regulate bone marrow centers, and if so, how should those regulations should be implemented.

## II. POLICY ANALYSIS

**A. Although FDA regulation of bone marrow transplantation may not have been necessary or even desirable in the past, FDA regulation will become increasingly important as the number of bone marrow centers grows.**

As long as the number of bone marrow centers is limited, as it is today)'<sup>28</sup> self-regulation of bone marrow centers is possible. The techniques of bone marrow transplantation were developed by highly-trained researchers in high-profile, established institutions. As bone marrow transplantation

<sup>28</sup> *Id*

<sup>29</sup> Standards, *supra* note 11.

<sup>30</sup> See *infra* text accompanying note 36.

becomes more widespread, however, the quality of physician performing the transplant may become more variable. FDA regulations would ensure that bone marrow centers are directed by experienced and competent physicians.

There may not have been a need for regulation when bone marrow transplantation was in its infancy, and indeed regulation at that time may have stripped research facilities of the flexibility to develop new techniques. While research facilities should continue to be given enough flexibility to develop new techniques, in general bone marrow centers should follow accepted standards for bone marrow transplantation. This will ensure some minimal level of safety for all bone marrow recipients and donors.

**B. The cost of failing to regulate is greater than the cost of regulating.**

The human and financial costs of unsafe methods of bone marrow transplantation are high. On the human side, for example, improper screening of donors or improper purging of marrow intended for autologous transplantation can result in death, imposing obvious human costs to patients and their loved ones. Financial costs are also high. For example, improper screening of donors may result in the transmission of infectious diseases, thus increasing health care costs. The human and financial costs of such tragedies are far greater than the cost of setting standards, certifying centers, and mandating regular inspections to assure compliance.

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**C. FDA should regulate bone marrow centers as soon as possible.**

Early regulation of bone marrow centers is more efficient than imposing a regulatory structure once bone marrow centers have proliferated. The example of the regulation of blood banks is instructive. In the late 1950's there were fewer than blood banks and the regulatory climate was somewhat relaxed.<sup>31</sup> In 1972 the Secretary of Health, Education, and Welfare transferred regulatory control over the blood banks from the Division of Biological Standards to FDA.<sup>32</sup> In 1973 FDA determined that all blood banks, including transfusion services, would be considered drug manufacturers.<sup>33</sup> As such, each facility – of which there were now 7,000 – would have to register with FDA and comply with applicable laws.<sup>34</sup> The regulatory burden on FDA was enormous.<sup>35</sup> The burden on the regulated facilities was great as well. Had the FDA regulatory scheme been in place twenty-five years earlier, each facility would have registered and complied with applicable laws from its conception. Compliance with the laws would have been integrated into the opening of the facilities and therefore would not have been

<sup>31</sup>J.M. Solomon, *The Evolution of the Current Blood Banking Regulatory Climate*, 34 TRANSFUSION 272, 273 (1994)

<sup>32</sup>*Id.* at 274.

<sup>33</sup>*.rd.*

<sup>34</sup>*Id.*

<sup>35</sup>*Id.*

as burdensome. Likewise, the burden on the government would have been spread out over time and would therefore have been much more manageable.

In 1988 there were between fifty and one hundred universities and hospitals in the United States performing bone marrow transplants)<sup>6</sup> The number of bone marrow centers is expected to increase dramatically. Regulations should be in place so that FDA and the regulated entities are not forced suddenly to cope with regulations which, had they been in place before the proliferation of bone marrow centers, would not have been unreasonably burdensome.

**D. Establishing basic standards of care will allow continued progress in learning about bone marrow transplantation.**

Considerable progress has been made in learning to perform bone marrow transplants, but much remains to be discovered about preventing the transmission of infectious diseases and preventing graft-versus-host disease. Standardized care will allow for the integration of data from bone marrow centers throughout the country,<sup>37</sup> thus allowing researchers to define better methods for bone marrow transplantation.

<sup>36</sup>DEEG, *supra* note 1, at 15.

<sup>37</sup>Rowe, *supra* note 6, at 143.

<sup>38</sup>*Id*

Acknowledging the need for uniform criteria, several organizations have come forward with their own proposals. These organizations include the Eastern Cooperative Oncology Group<sup>39</sup> and the American Society of Clinical Oncology, which published criteria together with the American Society of Hematology<sup>40</sup>. Though the medical community acknowledges the need for uniform standards, it is unlikely that the various groups will come together, along with NMDP, to establish such standards. FDA can facilitate the process by holding hearings at which the various groups can debate the parameters of sensible standards.

E. **FDA regulation should ensure that potential donors and recipients understand the risks involved and can make informed choices.**

FDA regulations should mandate disclosure of risks to recipients and donors and should allow both recipients and donors to make their own decisions regarding whether or not to participate in a transplant. Imagine, for example, a patient who is dying of leukemia and is in need of an allogeneic bone marrow transplant. This patient is one of the twenty to thirty percent<sup>41</sup> of patients who does not have an HLA-matched sibling donor. Registry searches uncover two

*The American Society of Clinical Oncology and American Society of Hematology Recommended Criteria for the Performance of Bone Marrow Transplantation*, 8 J. CLINICAL ONCOLOGY 563 (1990)

<sup>41</sup>Kernan, *supra* note 18, at 593.

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potential donors. One is a perfect imA match but carries an infectious disease. The other is free of infectious diseases but the HLA match is less than perfect. Although FDA regulations may counsel against a transplant involving either of these donors, ultimately the decision should remain with the patient.<sup>42</sup>

Although current NNDP standards afford a potential recipient wide latitude in making informed choices<sup>43</sup> they do not offer potential donors the same degree of freedom regarding whether or not to proceed with donation. According to the NMDP standards, The donor center medical director, the collection center medical director, or the [potential donor's] examining physician... may determine that abnormal findings [discovered during the medical examination of the potential donor] constitute unacceptable risk(s) to the donor.~ Thus, suppose a potential donor is a perfect match for a potential recipient. Suppose further that this donor is the only person on the registry with a suitable HLA match. A physician, not the donor, would make the final decision regarding whether or not the donation should take place. A better solution would be for the physician to appraise the potential donor of the risks involved and let him make his own decision regarding whether or not to proceed.

<sup>42</sup>Presumably there will be difficult insurance issues involved as well, but that is beyond the scope of this essay.

<sup>43</sup>NMDP Standards, *supra* note 29, at 9.421. *Mid.* at 9.310.

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FDA regulations should ensure that the donor is not pressured into proceeding with the bone marrow donation. Current NMDP standards mandate the availability of a disinterested Donor Advocate to counsel the potential donor about the risks of donating.<sup>45</sup> FDA regulations should likewise mandate the availability of such an advocate, particularly if the FDA regulations allow the potential donor greater latitude to determine for himself whether or not to proceed with donation at considerable risk to himself.

**F. FDA regulations should enhance fair competition among bone marrow centers.**

Maintaining minimal standards is important not only for the health of recipients and donors, but also for the economic well-being of bone marrow transplant centers. As discussed in Section A of this Part, quality control from within the medical community will become increasingly difficult as the number of bone marrow centers increases. Without regulations, bone marrow centers which cut costs by circumventing minimal standards will be able to provide services at a lower cost, yet consumers will not be aware of the substandard quality of care. Reliable bone marrow centers would benefit by FDA regulation because these centers would not be undercut by centers with lower standards.

Minimal standards should enhance fair competition, not restrict competition. In other words, regulations should not

<sup>45</sup>*Id.* at 7.000.

be so burdensome that small bone marrow centers are unable to open and operate. FDA should protect the public health, but it should do so in a sensible manner which does not restrict the availability or raise the cost of bone marrow transplantation.

**G. FDA should regulate process as well as product.**

The process by which bone marrow is extracted, treated, and transplanted should be regulated for several reasons. First, in contrast to drugs created in a lab, assessing the quality and safety of material which is derived from an organism is extremely difficult. Second, bone marrow is not stored for a long enough period of time to enable testing of the bone marrow itself. For **example, marrow** intended for an allogeneic transplant is infused the same day as it is harvested.

These policy considerations suggest that FDA should regulate bone marrow as a biological product rather than as a drug, because only if bone marrow is regulated as a biological product will FDA have authority to license bone marrow establishments as well as to license the product itself.<sup>48</sup> In this way, FDA can assure the integrity of bone

<sup>48</sup>See David A. Kessler, et. al., *Regulation of Somatic-Cell Therapy and Gene Therapy by the Food and Drug Administration*, 329 NEW ENGL. J. MED. 1169, 1171 (1993)

<sup>49</sup>Wallerstein, *supra* note 10, at 2271.

<sup>50</sup>For an excellent discussion of FDA's legal authority to regulate human organ transplants as drugs, medical devices, or biological products, see *Statement by the Food and Drug Administration Concerning its Legal Authority to Regulate* ID# 904—03—710

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marrow by regulating the *processes* by which it is procured, treated, and transplanted.

### H. **FDA should implement new regulations without disrupting the ongoing availability of bone marrow transplantation.**

During the development of any new licensing scheme, policymakers are faced with the question of retroactivity. For example, following the thalidomide tragedy, Congress passed the Drug Amendments of 1962.<sup>~</sup> Under these Amendments, FDA was required to determine affirmatively that new drugs were safe and effective.<sup>~</sup> FDA was given four years in which to approve drugs that had become available after 1938 but before the 1962 Amendments.<sup>51</sup> The Amendments grandfathered any drug that was available before 1938.<sup>52</sup> This example illustrates some of the possibilities available to FDA in implementing new bone marrow regulations.

Bone marrow transplantation has saved many lives. To take it off the market while FDA approves it would be heartless. On the other hand, grandfathering existing bone marrow centers would not give FDA the degree of control it

*Human Organ Transplants and to Prohibit their Sale: Hearing*

*Before the Subcommittee on Investigations and Oversight,*

*House Committee on Science and Technology*, 98th Cong., 1st

Sess. (1983), reprinted in PETER BARTON HUTT & RICHARD A.

MERRILL, **FOOD AND DRUG LAW** 693 (2d ed. 1991)

<sup>49</sup>HUTT, *supra* note 47, at 478.

<sup>~</sup>*Id.*

<sup>51</sup>*Id.*

<sup>52</sup>*Id.*

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should exercise over these centers. A reasonable compromise would be similar to the one reached in the approval of new drugs. All new bone marrow centers would have to be licensed by FDA. Existing centers would have to be licensed within a specific time frame, but could continue to operate as usual in the meantime.

An alternative procedure for implementing new bone marrow regulations would be for FDA formally to promulgate regulations requiring the licensing of *all* establishments but tacitly to allow existing centers to continue their work without scrutiny. For two reasons, however, FDA should not pursue such a policy. The first reason is a legal one. In *Heckler v. Chaney* the Supreme Court held that FDA refusal to take enforcement steps is presumptively not reviewable.<sup>54</sup> *Chaney* left open the question, however, of whether an agency's rules might under certain circumstances provide courts with adequate guidelines for informed judicial review of decisions.<sup>55</sup> At least one court has determined that this reservation, along with the basic tenet of administrative law that an agency is bound to follow its own regulations, rendered FDA inaction reviewable despite *Chaney*.<sup>55</sup> Thus, FDA would face some risk that failure to enforce regulations against existing centers would be reviewable. The risk of

<sup>54</sup> 470 U.S. 821, 831 (1985)

<sup>54</sup> *Id.* at 836.

<sup>55</sup> *Heterochemical Corp. v. Food and Drug Admin.*, 664 F. Supp. 271, 274 (E.D.N.Y. 1986)

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such an outcome is slight, however. A better reason for not pursuing this approach is that as a matter of policy, agencies should attempt to be as forthright as possible. Being forthright helps regulated parties to plan and fosters confidence that FDA is at least trying to be fair and well-reasoned.

### **III. CONCLUSION**

Government regulation of bone marrow transplantation would protect the public health while at the same time creating a level playing field among bone marrow centers. Because of its experience regulating blood, FDA is the most reasonable candidate to promulgate and enforce such regulations. According to Craig W.S. Howe, chief executive officer of NMDP, it is only a matter of time before FDA starts regulating bone marrow.<sup>57</sup> FDA should begin the regulation process now, before a crisis and before bone marrow centers proliferate. In addition, FDA should take a well-reasoned approach to regulation of bone marrow centers so that its efforts to protect the public health do not inadvertently injure the public health by decreasing the availability or increasing the cost of bone marrow transplantation.

<sup>56</sup> *See generally* Solomon, *supra* note 31 (tracing the evolution of the current blood banking regulatory climate). <sup>57</sup> Personal communication (Jan. 11, 1995)

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